REMARKS

Information Disclosure Statement

The Examiner has indicated that the listing of references included in the specification is "not a proper information disclosure statement." Applicants wish to thank the Examiner for bringing this to their attention. In response to this, Applicants submit herewith a Third Information Disclosure Statement under 37 C.F.R. §1.97 including the three references listed in the specification that were not already included on the first two Information Disclosure Statements mailed on November 12, 2003 and March 29, 2004.

The Oath/Declaration

The Examiner has indicated that a new declaration is required due to an altered zip code for Inventor Witztum and a dual date entry for Inventor Palinski. In response to this, Applicants submit herewith for consideration a properly executed replacement declaration.

Objection to the Specification

The Examiner indicates that the specification is objected to for lacking a reference to issued Patent No. 6,716,410. Accordingly, Applicants have amended the specification to properly recite that the instant application "is a continuation application of US Patent Application Serial Number 09/699,131, which was filed on October 26, 2000, and which issued as U.S. Patent No. 6,716,410 on April 6, 2004,..."

Claim Objections

Claims 30 and 32 stand objected to as depending on canceled claims. These claims have been canceled herein, without prejudice, to facilitate prosecution. Accordingly, this objection no longer applies.

Claim 29 also stands objected to for containing "a typo." Likewise this claim has been canceled herein, without prejudice, to facilitate prosecution.

Claim 31 also stands objected to for an inappropriate reference to sequence listings, which has been corrected herein.

Rejection of Claims 29-32 Under 35 U.S.C. §112, Second Paragraph

The Examiner has indicated that claims 29-32 are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More particularly, the Examiner has indicated that claim 29 is vague and indefinite because it does not say what the antibody is specific for. Accordingly, claim 29 has been canceled and the remaining claims (27 and 31) now precisely recite what the antibody does and does not bind to. Accordingly, this amendment does not introduce new matter.

Claim 31 has been indicated to be vague and indefinite for including the word "of." Applicants thank the Examiner for the suggestion to remove this word for clarity and have done so herein.

The term "fragment thereof, fragment antibody, and single chain fragment" in claims 28, 30 and 32 are said to be "relative terms." However, Applicants contend that Fabs and scFvs to which the remaining independent claim has been limited have special meaning in the antibody field and would not be considered indefinite. These terms would easily be understood to have special meaning in the immunology arts and would reasonably apprise anyone of skill in these arts as to the scope of the instant invention. Accordingly, Applicants respectfully request reconsideration of this ground for rejection.

35 U.S.C. §101

The Examiner has rejected claims 27-32 as being drawn to non-statutory subject matter. However, as amended herein, Applicants believe that this rejection no longer applies.

35 U.S.C. §112, First Paragraph

The Examiner indicates that claims 27-32 are rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connection, to make and/or use the invention." In particular, the Examiner reasons that "[t]he claims fail to provide the identity or structure of this antibody recognition site."

In addition, the Examiner alleges that the claims lack an adequate written description.

As amended herein, the claimed antibodies (and fragments) have four structural characteristics:

1) They are specific for oxidation specific epitopes found on copper-induced oxidized low density lipoprotein (Cu-OxLDL).
2) They are specific for oxidation specific epitopes found on malondialdehyde low density lipoprotein (MDA-LDL).
3) They do not bind to native LDL.
4) They inhibit uptake of Cu-OxLDL by macrophages.

It would be well within the capacity of a person of skill in the art to select antibodies on the basis of meeting these criteria based on the teachings included in the specification. Such antibodies are thought to function by blocking uptake of OxLDL by macrophages which inhibits the formation of foam cells (page 18, lines 32-33.) The exact structure of such selected antibodies and their binding sites could easily have been determined based on the level of skill in the art know at the time of filing based on routine high-throughput screening experiments.

The Examiner bases the alleged requirement that "[t]he nucleic acid structure is required" to meet the written description requirement on *Fiers v. Revel,* 25 USPQ 2d 1601 at 1606 (Fed. Cir. 1993) and *Amgen v. Chugai Pharmaceuticals Co., Ltd.,* 18 USPQ 2d 1016 (Fed. Cir. 1991).

The court held in *Fiers* that, "what is needed to meet the description requirement will necessarily vary depending on the nature of the invention claimed." (*Fiers, supra,* at 1170.) In *Fiers* and in *Amgen,* the claimed invention was a DNA encoding a particular protein. In contrast, the instant invention is a method of using an antibody having specifically enumerated structural characteristics. Applicants request the Examiner to consider that antibodies are not the same as nucleic acids in terms of what is necessary to establish that they are adequately described under 35

U.S.C. §112, first paragraph.

In further support of this ground for rejection, the Examiner recites that "[t]he instant specification and claims describe an isolated monoclonal antibody by its protein function, however this description does not describe the claimed antibody itself. See also, *In the [Regents] of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412,...)". Again, the Examiner is citing cases holding that claims to DNA were unpatentable as lacking an adequate written description.

In two more recent court decisions, the patentability of antibodies has been reviewed. In *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the claims at issue were directed towards monoclonal antibodies that targeted the CD40CR antigen expressed by activated human T cells. In *Noelle*, the Federal circuit stated, "the PTO would find compliance with 112, §1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well-defined structural characteristics of antibody binding, and the fact that the antibody technology is well developed and mature" (*Noelle, supra,* at 1349 (quoting *Enzo Biochem v. Gen-Probe, Inc.,* 323 F.3d 956, 970 (Fed. Cir. 2002).) In *Noelle,* claims which recited a genus of antibodies that bound to a mouse antigen were found to be unpatentable, because the corresponding human antigen had not been adequately characterized. However, in the instant case, the characteristics of the antigen are specified – the antigen is found on Cu-OxLDL, MDA-LDL, but not on normal LDL, and the antigen is recognized by macrophages. It is not necessary that the antigen be characterized to the level of amino acid sequence, since modern techniques of high throughput screening and molecular modeling could have easily been employed to do so at the time the application was filed. In fact, even as early as 1997, epitopes on the surface of macrophages that bind to OxLDL were well known in the literature. See Attachment A hereto.

The Examiner additionally opines that the Applicant "provides no guidance as to what modifications or structure are important for the predictable function of the monospecific antibody." However, Applicants submit that this standard is presently too harsh, given the advances in technology since the cases that the Examiner is relying on were decided. As recited above, the court in *Noelle* held that the PTO would find compliance with the written description requirements for a claim to an antibody capable of binding to a particular antigen, "in light of the well defined structural

characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature" (*Noelle, supra*, at 1349.) Accordingly, Applicants respectfully request reconsideration of this position.

In conclusion, Applicants submit that claim 27, and claim 31 which depends thereon, are adequately enabled and described in the instant specification.

35 U.S.C. §112, First Paragraph – Claims 28, 30, 32

These claims are additionally rejected under 35 U.S.C. §112, first paragraph. However, these claims have been canceled herein, without prejudice, to facilitate prosecution. Accordingly, this ground for rejection no longer applies.

Double Patenting

The Examiner finds that the instant specification is subject to a double patenting rejection over claims 8-12 of U.S. Patent No. 6,375,925 (the '925 patent.) However, Applicants respectfully disagree with this ground for rejection over the '925 patent.

The '925 patent describes and claims antibodies that bind to specific epitopes of MDA2 and NA59 in plaque. These are "oxidation-specific epitopes" in oxLDL (col. 4, lines 25-39.) These epitopes are completely different. MDA2 antibodies target malondialdehyde-lysine, and NA59 antibodies target 4-hydroxylnonenal(4-HNE)-lysine (col. 5, lines 1-5.) Accordingly, although they are each described as demonstrating "binding characteristics which are almost identical" (col. 5, line 29), their specificity is entirely different. Moreover, the antibodies of the present invention that cross-react with both MDA-LDL and Cu-OxLDL do "not bind significantly to 4-HNE-LDL. Accordingly, the presently claimed antibodies are entirely different from the antibodies described and claimed in the '925 patent. As amended herein, the claimed antibodies are neither taught nor suggested by the '925 patent. Indeed, the '925 patent is directed towards the production of antibodies that are specific for a single epitope on an oxLDL – this teaches away from the production of an antibody that cross reacts with two or more epitopes as is presently claimed.

Rejection Under 35 U.S.C. §102(e)

The Examiner has indicated that claims 27-32 are unpatentable under 35 U.S.C. §102(e) over Witztum et al., U.S. Patent No. 6,225,070 ('070.) More particularly, the Examiner reasons that the mouse monoclonal antibodies, E06, E013, E014 and E017, anticipate the recited claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987.) The monoclonal antibodies that are claimed and described in the '070 patent are produced in apolipoprotein deficient mice. They all have differential binding to LDL associated epitopes, but none is selected to be specific for MDL-LDL and Cu-OxLDL. Any cross-reactivity between antibodies is merely incidental, and does not constitute "specificity".

For example, E06 is characterized as being specific for Cu-OxLDL, but is also shown to bind to MDA-LDL, but only if it is greater than 70% oxidized. Also, E06 is shown to bind to native LDL (Table I). As indicated in Table II, E06 is best used as a determinant of circulating LDL, whereas the antibodies of the present invention are targeted towards plaques. The other antibodies mentioned by the Examiner (E013, E014 and E017) also have differential affinities for varying combinations of epitopes. However, none of the antibodies described or suggested in the '070 patent have the specificities required by the instantly claimed invention. For this reason, the '070 patent does not anticipate the claimed invention.

Rejection Under 35 U.S.C. §102(b)

Claims 27-32 stand rejection under 35 U.S.C. §102(b) as being anticipated by Sotiriadou, et al. However, this reference refers to an antibody named "Delta-IK17" that binds to a protein expressed on lymphocytes, which is correlated with ontogenesis. This is simply a case of an antibody designation being confusingly similar with that chosen by the Applicants. Applicants' claimed IK-17 antibody as presently claimed and described binds to macrophages, not lympocytes. Accordingly, Applicants respectfully request that this ground for rejection be reconsidered.

SUMMARY

If the Examiner believes that it would facilitate prosecution, Applicants' Attorney, Laurie A. Axford, may be contacted at (619) 230-7714 or at laxford@gordonrees.com.

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-1990 and please credit any excess fees to such deposit account.

Respectfully submitted,

Dated: July 12, 2006

By: _____
Laurie A. Axford
Registration No. 35,053

Please recognize our Customer Number 27111 as our correspondence address.

GORDON & REES, LLP
101 West Broadway, Suite 1600
San Diego, California 92101-8217
Phone: (619) 696-6700
Facsimile: (619) 696-7121
Attorney Docket No. XUCSD-1034917